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RESEARCH ARTICLES

Management of platinum-resistant ovarian cancer with the combination of pemetrexed and gemcitabine

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Abstract
Introduction Platinum resistant ovarian cancer is a current challenge in Oncology. Current approved therapies offer no more of a 20% of response. New therapeutic options are urgently needed.
Patients and Methods Patients were treated with the combination of Pemetrexed 500 mg/m^2 d1 and Gemcitabine 1000 mg/m^2 d1,8 in a 21 days basis.
Results 10 platinum-resistant ovarian cancer patients were treated under compassionate use. Mean previous chemotherapy lines were 3.3. Mean administered cycles were 4. Mean CA 125 decrease was on average of 47%, with one patient experiencing a 95% decrease in her CA 125 level. 1 patient had a complete clinical remission, and 2, had partial radiological responses. Mean Progression free survival was 16.5 weeks, and Overall Survival was 21.2 weeks. Treatment was well tolerated.
Conclusions Deemd to the observed activity, the combination of Pemetrexed and Gemcitabine deserves deeper investigation in platinum-resistant ovarian cancer patients.

Keywords Ovarian cancer · Platinum-resistant · Pemetrexed-Gemcitabine

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Introduction

Ovarian cancer is the most common cause of death among women with gynaecologic malignancies, and the fifth leading cause of cancer death in women in the United States [1]. Approximately 22,430 American women are diagnosed with ovarian cancer annually. Of these women 75% present with stage III or IV, and an estimated 15,280 die of their disease.

The recommended therapeutic approach to these women is surgical cytoreduction followed by systemic chemotherapy with a platinum agent plus paclitaxel. The most important predictors of relapse and the need for salvage or second-line therapy are clinical stage and bulk of disease. Other characteristics associated with an increased likelihood of persistent or recurrent disease are clear cell histology, poorly differentiated histological grade, poor performance status, non-platinum-based initial treatment and larger residual tumour volume of the presence of ascites at the time of surgical cytoreduction.

The selection of salvage therapy is commonly based upon whether women are "sensitive" or "resistant" to initial platinum-based treatment. Patients who respond to initial

platinum-based therapy and have a significant relapse-free interval (more than six months) have a high probability of responding again to platinum-based treatment at the time of relapse. These patients are termed "platinum-sensitive". The length of the prior response is highly predictive of the upper limit of the duration of disease control that can be expected with second-line cisplatin-based chemotherapy [2]. In contrast, patients with platinum-resistant disease have the following characteristics listed in Table 1.

Such women do not generally respond to second-line platinum-based therapy. They have a poorer prognosis, and should be considered for salvage therapy with non-cross-resistant agents. Successful management of women who are platinum-resistant requires the use of non-cross-resistant agents. Single-agent therapy is usually chosen. Although combination regimens are associated with somewhat higher objective response rates and a two to three month improvement in progression-free survival (PFS), they are also more toxic, and no regimen has produced a survival benefit compared to single-agent therapy.

At least 10 drugs are active, including paclitaxel, docetaxel, oral etoposide [3, 4], liposomal doxorubicin [5, 6], topotecan [7, 8], gemcitabine (G) [9, 10], vinorelbine [11, 12], ifosfamide [13, 14], leucovorin-modulated 5-fluorouracil [15], hormonal treatment with tamoxifen [16] with or without medroxyprogesterone acetate [17], and aromatase inhibitor [18]. More recently bevacizumab, a humanised monoclonal antibody that targets vascular endothelial growth factor (VEGF), has shown activity for platinum-refractory ovarian cancer, both alone [19, 20] and in combination with cytotoxic chemotherapy [21, 22], although the side effect profile can be problematic [23, 24]. But independently of the chosen regimen, long-term survival remains poor.

The significant benefit of combination chemotherapy for cancer patient response rates has made the development of relevant preclinical models an active area of oncology research. Although useful combinations are usually discovered empirically, there have been many attempts to design models that rationally describe drug combinations. Often, drug combinations consist of two drugs with distinct but complementary biochemical mechanisms. Because of the defined nature of antifolate enzyme inhibition, antifolates have been the focus of numerous combination studies and modelling.

Pemetrexed disodium (P) is a multi-targeted folate antimetabolite (MTA) that primarily inhibits thymidylate synthase (TS) and also inhibits additional folate-dependent enzymes such as dihydrofolate reductase (DHFR), a main target of methotrexed, and glycinamide ribonucleotide formyltransferase (GARFT) [25]. Inhibition of TS and DHFR results in decreased thymidine, while inhibition of DHFR and GARFT results in disturbance of purine metabolism in DNA synthesis. MTA enters cells mainly via the reduced folate carrier 1 (RFC1) [26], and is an optimal substrate for folylpolyglutamate synthetase (FPGS). FPGS converts the drug to the predominant pentaglutamate form that leads to an enhanced intracellular retention of the drug and more potent inhibition of TS, DHFR and GARFT than the monoglutamate form. This agent is broadly active in a wide variety of solid tumours, including non-small-cell lung [27], breast [28], bladder [29], head and neck [30], and ovarian cancers [31], as well as mesothelioma [32].

Table 1 Characteristics for patients with platinum-resistant disease

1. Progression during platinum-based therapy
2. Stable disease as the best response to prior platinum-based therapy
3. Relapse less than six months after completion of prior platinum

Preclinical studies suggested that the combinations of P with cisplatin, as well as taxanes and G, produce additive or synergistic cytotoxicity [33]. Synergistic activity of G and P has been described in colon cancer cell lines [34], where P increased the cytotoxicity activity of G; a possible schedule-dependent cytotoxicity in cell lines [35] has also been suggested, but with contradictory results in a phase I trial [36]. The potential synergistic effect has been studied in bladder cancer cell lines and *in vivo* in bladder cancer patients [37] where the interaction between G and P was synergistic; indeed, P favoured G cytotoxicity by increasing cellular population in the S-phase, reducing Akt phosphorylation as well as by inducing the expression of a major G uptake system, the human equilibrative nucleoside transporter-1 (hENT1), and the key activating enzyme deoxycytidine kinase (dCK) in both cell lines. The potential synergistic effect has been shown also for pancreatic cell lines [38].

Experience with P and G combinations is scarce, but promising activity has been shown [39–41]. The most relevant study is that published by Hensley et al. [41], which included 16 platinum-resistant patients and recorded 27% objective responses.

So we decided to initiate a compassionate use programme for the combination of P and G in highly pretreated platinum-resistant ovarian cancer patients after failure of standard approaches.

Material and methods

Inclusion criteria for patient population

To be treated in this programme, patients were required to have platinum-epithelial ovarian cancer with disease measurable by the Response Evaluation Criteria in Solid Tumors (RECIST) criteria [42] or evaluable with CA-125. Patients were required to be considered platinum-resistant as described in Table 1 and there was no restriction on the number of prior therapies. Patients with progression during previous chemotherapy were also included. Prior therapy with a taxane was required.

Participating patients were required to have adequate bone marrow (absolute granulocyte count .1500/μl and

platelets ≥100,000/μl), renal (serum creatinine <1.5 times the upper limit of normal [ULN]) and hepatic (bilirubin ≤1.5 times ULN and ALT or AST ≤3 times ULN) function. Patients were required to have provided written informed consent consistent with current institutional and government regulations for compassionate use treatment acceptance.

All treated patients were included in the analyses of response, PFS and overall survival (OS), which were our main study end points.

Study design and treatment schedule

Patients were treated with intravenous P 500 mg/m^2 on day one and G 1000 mg/m^2 on days one and eight. These agents were reconstituted in sodium chloride solution prior to use. G 1000 mg/m^2 was given intravenously in 250 ml of normal saline over 30 min on days 1 and 8 and P 500 mg/m^2 was given intravenously in 100 ml of normal saline over 10 min, 90 min after the end of G infusion on day 1 of a 3-week cycle; 400 μg of folic acid was given orally daily and 1000 μg of vitamin B_{12} was given intramuscularly every 9 weeks starting 7 days prior to the first dose and until 3 weeks after the last dose of P; 4 mg of dexamethasone was given orally every 12 h on the day before, day of and day after all doses of P. We adopted this schedule, adjusting both drugs to their main extended use and approved schemas.

Antiemetics were given before chemotherapy on days 1 and 8 according to the National Comprehensive Cancer Network (NCCN) guidelines. Colony-stimulating factors were not used prophylactically to prevent granulocytopenia. Treatment continued until disease progression, unacceptable toxicity or two cycles beyond identification of a complete response (CR). All toxicities were graded according to the National Cancer Institute Common Toxicity Criteria (version 2.0). Treatment was continued until the patient experienced tumour progression, grade 3 or 4 toxicities or patient request/physician discretion. Continuous treatment with P+G was allowed until toxicity, tumour progression, patient request or physician decision. Any limit in the number of cycles was established.

Table 2 Patients' characteristics

Age
Range: 48–72 years
Median: 62.8 years
ECOG
PS0: 2 patients
PS1: 5 patients
PS2: 2 patients
PS3: 1 patient
No. of previous chemotherapy lines
2 lines: 1 patient
3 lines: 5 patients
4 lines: 4 patients
Median: 3.3 lines
Patients progressing during previous chemotherapy
Total: 3
1 patient with liposomal doxorubicin
2 patients with topotecan
Histology
Endometrioid: 4 patients
Undifferentiated: 1 patient
Squamous: 1 patient
Papillary: 1 patient
Signet ring: 1 patient
Serous-papillary: 1 patient
Initial stage
IC: 1 patient
IIC: 1 patient
IIIA: 1 patient
IIIC: 5 patients
IV: 2 patients
Sites for metastatic disease
Pleural effusion in the two stage IV patients
Patients negative for CA-125: one
Number of cycles administered.
Range: 1–6
Median 4
Global response
Progression disease: 3 patients
Stable disease: 3 patients
Partial response: 3 patients
Complete response: 1 patient
Response by RECIST criteria
1 complete (alive patient)
2 partial (alive patients)

Efficacy

CA-125 was determined every first day of the cycle, and controls for the 8th day included history and blood test count. RECIST criteria were used to evaluate response when existing lesions could be measured radiologically [42]. CR was defined as the disappearance of all target and nontarget lesions, no evidence of new lesions and reduction of CA-125 of more than 50%, lasting at least 4 weeks. Partial response (PR) was defined as a 30% or greater reduction in the sum of the longest dimensions of all target lesions and no unequivocal progression of nontarget lesions, lasting at least 4 weeks. Progressive disease (PD) was defined as a 20% or greater increase in the sums of the longest dimensions of target lesions, or the appearance of new lesions within 8 weeks of study entry. Stable disease (SD) was defined as any condition not meeting the above criteria. Changes in CA-125 alone were used to determine tumour response or progression, when it could not be radiologically determined, following Rustin's criteria [43].

PFS was defined as the time from the first day of treatment to the first observation of disease progression or death due to any cause or last follow-up. PFS was censored for patients who were alive and free of progression at time of last follow-up.

OS was defined as the time from the first day of treatment to the time of death due to any cause; patients remaining alive at their last follow-up were censored at that time.

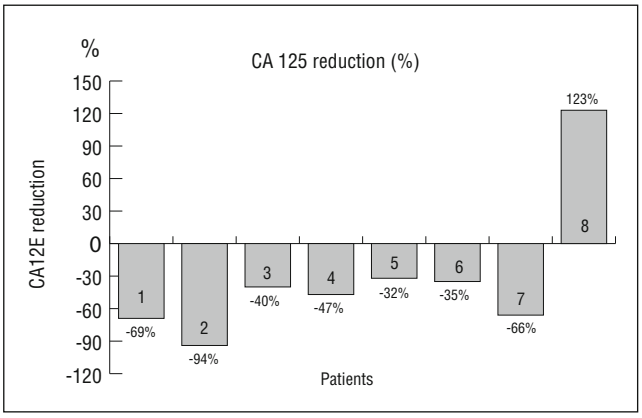

Fig. 1 CA-125 reduction for all of the cohort

Results

Between June 2007 and February 2008 a total of 10 patients were enrolled in this programme. Patients received at least one cycle of chemotherapy. As of April 2008, there were two objective responses and enrolment continues.

Demographic and baseline characteristics are presented in Table 2. Patients had a mean age of 62.2 years, 70% of the patients had a baseline ECOG PS of zero and one. Nine patients (90%) had previously received at least three lines of chemotherapy and three of them progressed during the previous chemotherapy schedule. Forty percent of the patients had endometrioid tumours and only one patient had serous histology. No patient had bulky disease. Two patients had metastatic disease, with documented malignant pleural effusion. All patients had platinum-resistant disease. One patient was CA-125 negative.

Patients received a median of four cycles of chemotherapy (range, one to six). CA-125 was able to be measured in eight of the ten patients (CA-125 value was negative in one patient and the other patient died before the 2nd measurement). The reduction of this biomarker was, on average, 47%, with one patient treated on the fifth line with a reduction of more than 95% (Fig. 1).

Of the treated patients, two presented PRs by RECIST criteria, and one of these had a complete radiological response.

Table 3 Toxicities

Haematological toxicities
Neutropenia
Grade 3: one patient
Grade four: one patient
Anemia
Grade 2 : one patient
Non-haematological toxicities
Asthenia
Grade 2: two patients
Digestive
Grade one: one patient

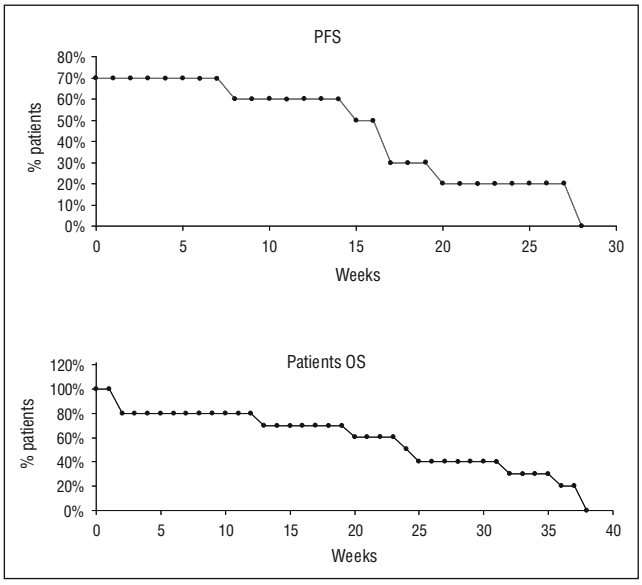

Fig. 2 PFS and OS for the whole cohort

PFS for the responding patients (partial and complete) with SD was 16.5 weeks (censored data) and OS was 21.2 weeks (censored data), with three patients alive today, two with disease and one free of disease (Fig. 2).

Toxicities

Any adverse event deemed at least possibly related to treatment was defined as a toxicity and is included in these analyses. Toxicity data were available for all patients (Table 3). The frequency and severity of grade 3 and 4 toxicities are shown in the table.

Haematological toxicity

Neutropenia and anaemia were the most common and severe haematological toxicities. Without prophylactic colony-stimulating factor support, two of the patients had absolute neutrophil count nadir values constituting grade 3 toxicity, and grade 4 toxicity without febrile neutropenia. Grade two anaemia was coincident in the same patient with grade 4 neutropenia. Thrombocytopenia was not recorded in our group.

Non-haematological toxicity

Among the grade 3 and 4 non-haematological toxicities, there was grade 3 asthenia in one patient and grade 2 in two other patients. Another relevant toxicity was grade 1 nausea and vomiting.

Grade 3 and 4 toxicities led to a 25% reduction in the total dose administered and prophylactic use of G-CSF.

Discussion

It is well established that ovarian cancer is a chemotherapy-sensitive tumour, but the survival for platinum-resistant patients remains poor. The goals of therapy for patients with recurrent ovarian cancer are to improve quality of life and extend survival. Results of the recommended chemotherapies for platinum-resistant disease show a response rate of around 20% [44].

The synergic effect of P and G observed in preclinical studies, and the reported clinical activity in ovarian cancer of both of the agents, provided the rationale for combining these two agents in highly pretreated platinum-resistant ovarian cancer.

The present report describes a compassionate use programme of P in combination with G in the treatment of 10 patients with platinum-resistant ovarian cancer, who had received prior taxane and platinum combinations in the adjuvant or metastatic setting, and/or had progressed during previous standard chemotherapy schedules for platinum-resistant disease.

We found an interesting result of 3 responses by RECIST criteria; one is complete and this patient is alive without any evidence of disease recurrence (CR). Of the two partial responders by RECIST criteria, both are alive with disease. Three of our patients were considered SD and the PFS for the responding patients was 16.5 weeks with an OS of 21.2 weeks. Three of the patients are alive today, two with disease and one free of disease. Toxicities have been shown to be mild and manageable. Results in the CA-125 level control were also remarkable.

We find it difficult to offer a good explanation for these unexpected good results. In our group we have only one patient with serous histology and no patient had bulky disease. The complete responder patient was negative for CA-125 and her histology was endometrioid. We cannot exclude the existence of a clinically relevant synergistic effect for the combination, which also was suggested by the previous work of Hensley et al [41]. From our point of view, this combination should be tested in clinical trials to confirm its efficacy. We will continue treating platinum-resistant patients with this combination.

Conflict of interest The authors declare no conflict of interest.

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